Remarks

Amendments to the Claims

The amendments to the claims more particularly identify the antibodies that bind to identified cleavage products that arise from calpain and/or caspace-3 proteolysis. No new matter has been added. Support for the claims can be found at least at page 6 and in example 4 on page 22.

Status of the Claims

Claims 1-20 have been withdrawn from consideration. Claims 21-25, 28-34, 36 and 37 have been amended. Claims 38-49 have been added.

Upon entry of the amendments, claims 21-49 will be presented for consideration.

OBJECTIONS TO THE SPECIFICATION

The title of the application has been objected to as being nondescriptive. Applicants have amended the title in response to the Examiner's suggestion.

The reference to the prior provisional application is objected to for listing an incorrect filing date. Applicants have corrected the filing date.

OBJECTION TO THE CLAIMS

Claims 22 and 31 are objected to for not having a period at the end of the claim. Correction has been made.

REJECTIONS UNDER 35 USC §112

Claims 21-24, 26-33 and 35-37 are rejected under 35 U.S.C. §112, first paragraph as failing to reasonably convey to one skilled in the relevant art that at the time of filing the application, the inventors had possession of the claimed invention. The detection of spectrin breakdown products is asserted not to be supported by use of any agent; rather that the specification teaches the use of antibodies to identify spectrin and its breakdown products.

Applicants, in the interest of progressing the claims to allowance, have further defined the "agents" that specifically bind spectrin and its breakdown products as antibodies directed to the

breakdown products. It is believed that the amendments are responsive to the written description requirement and the Examiner is respectfully requested to withdraw the rejection.

Claims 23 and 32 are rejected under 35 U.S.C. §112, second paragraph as indefinite for failing to particularly point out and distinctly claim the subject matter regarded by applicants as the invention. The Action finds that agents that do not bind at least one SBDP are unduly numerous and therefore do not appropriately indicate metes and bounds of the claimed invention.

Applicants have amended claims 23 and 32 to more closely focus on the type of agents that specifically bind to the spectrin breakdown products. The amendments are believed to be responsive to the Examiner's concerns and withdrawal of the rejection is respectfully requested.

REJECTION UNDER 35 USC §103

Claims 21-37 are rejected under 35 U.S.C. §103(a) as unpatentable over Lynch, *et al.* The Action takes the position that because Lynch, *et al.* recite methods to detect spectrin breakdown products as set forth in withdrawn claims 1-20 in the instant application, the method of using the products is anticipated and use of the composition for performing the method is obvious. The Action further states that Lynch, *et al.* synthesized antibodies against naturally occurring spectrin breakdown products, which were used for the claimed method. Accordingly, the Action believes that the spectrin breakdown products are the same as those recited in claims 21-37.

Applicants have reviewed the Lynch, *et al.* publication with special attention to any description of spectrin breakdown products, identity of those products and use of the breakdown products in the methods for detecting cellular death in a subject.

It appears that Lynch, *et al.* determined that spectrin levels are elevated subsequent to injury and that two polypeptide products, so-called BDP1 and BDP2 (150kDa and 155kDa), arise when the protease calpain degrades the spectrin. The scientists prepared a polyclonal antibody to spectrin, which could also detect the two BDPs. There is no mention either that other breakdown products existed or that the Lynch polyclonal antibody would detect those other breakdown products.

Lynch, *et al.* showed only that the antibody to spectrin could be used to detect 150 and 155 kDa products produced by calpain proteolytic cleavage. Even if the spectrin antibody did or could detect other calpain breakdown products, Lynch, *et al.* used the SAME antibody to detect both BDP1 and BDP2 and spectrin. This antibody was not selective for spectrin, BDP1 or BDP2; rather, it bound to all three proteins.

Applicants believe that preparing and using antibodies selective only for spectrin, an antibody selective only for 150kDa, an antibody selective for only 150ikDa, an antibody selective only for 145kDa and an antibody selective only for 120 kDa would be an obvious way for the skilled person to use the information in the Lynch, *et al.* reference. Lynch, *et al.* did not suggest that individual antibodies specific for 120, 145, 150 and 150i kDa BDPs would be a choice for analyzing the breakdown of spectrin; in fact, the 145kDa product was not identified and Lynch, *et al.* detected only calpain cleaved 150 and 155 kDa products.

Lynch, *et al.* describe a method of detecting cellular breakdown and do so by detecting increased levels of spectrin and two major breakdown products. Lynch, *et al.* speculate that one might be able to isolate antibodies directed to "hidden" epitopes, or to make monoclonals, that react only with the two breakdown products; however, the meaning of "hidden" is not entirely clear and there is no description to identify the structure of these epitopes or how the skilled artisan would attempt to find the epitopes. The Lynch, *et al.* results describe the detection of significant levels of BDPs above a basal level to confirm cell death or degradation. Applicants, on the other hand, have provided a method to analyze the breakdown product distribution by distinguishing relative amounts of identified spectrin breakdown products arising from calpain, caspase or both proteolytic enzymes.

Accordingly, Applicants submit that the method described by Lynch, *et al* is neither the same nor obvious as that disclosed by Applicants. The purpose of the Lynch method is to determine injury to the nerve cells; the purpose of Applicants' method is to selectively measure and monitor the proteolytic breakdown products of spectrin by calpain and caspase-3, a method that utilizes antibodies that specifically bind to spectrin cleavage products and, depending on amount and type of product provides information on type of nerve damage; *i.e.*, differentiates between

spectrin BDPs arising from calpain or caspase-3 cleavage (please refer to page 6, lines 1-27 in the application).

Applicants conclude that Lynch, *et al.* do not even mention the 145, 120 and 150i kDa BDPs or even state that there are specific breakdown products of caspase-3 to which specific antibodies might be prepared. The spectrin breakdown products discussed by Lynch, *et al.* are quite clearly different from those identified and used by Applicants to prepare the antibodies.

SUMMARY

Applicants respectfully traverse rejection of the claims based on written description and as obvious over the cited reference.

It is believed that all concerns have been addressed and that a complete response has been submitted. No fee is believed to be due in connection with this response; however, should any fees be due, the commissioner is authorized to deduct such fees from Saliwanchik, Lloyd & Saliwanchik Deposit Account No. 19-0065. Should any issues remain or should the Examiner believe that a telephone conference with Applicants' attorney would be helpful in expediting prosecution of this application; the Examiner is invited to contact the undersigned at 352.375.8100.

Respectfully submitted,

Barbara S. Kitchell

Barbara S. Kitchell
Patent Attorney
Registration No. 33,928
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: Saliwanchik, Lloyd & Saliwanchik
A Professional Association
P.O. Box 142950
Gainesville, FL 32614-2950

BSK/lkw
Enclosure: Amendment Transmittal Letter (1 page)